# Specialty Conference

# Recent Trends in the Management of Life-Threatening Ventricular Arrhythmias

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Significant advances have recently been made in understanding the mechanisms and the rationale of therapy for ventricular arrhythmias responsible for sudden death. The mainstay of therapy remains pharmacologic but surgical intervention and implantable electronic devices hold considerable promise. Programmed electrical stimulation of the heart permits the electrophysiologic mechanism of the arrhythmia to be established in many instances; the suppression of the inducible arrhythmia by various classes of electrophysiologic agents may provide a reliable index for predicting long-term therapy. The pharmacologic suppression of complex ectopy is also predictive of long-term efficacy but its relation to the suppression of inducible arrhythmia is not defined. Particularly significant is the development of new antiarrhythmic agents such as amiodarone. Amiodarone lengthens cardiac repolarization and has a powerful suppressant effect on spontaneously occurring arrhythmias but less so on inducible ventricular tachycardia. It has a significant potential to prolong life in patients with life-threatening ventricular arrhythmias. Further advances in electropharmacology and surgical treatment of ventricular arrhythmias and in implantable devices are imminent.

BRAMAH N. SINGH, MD, PhD:* The treatment of life-threatening ventricular arrhythmias has recently undergone significant changes. The current therapeutic trends are beginning to assume an increasingly rational basis with a shift away from the essentially empirical approach that has dominated antiarrhythmic therapy for many decades. The newer advances that have contributed to this growing trend should reduce the mortality for patients with malignant ventricular tachyarrhythmias.[1] Electrophysiologic studies in isolated tissues and in intact animals have shown that most ventricular arrhythmias arise on the basis of reentry and less commonly on the basis of abnormal automaticity, spontaneous or triggered as a result of early or late afterdepolarizations.[2] However, the present diagnostic approaches still do not permit the unequivocal determination of the electrophysiologic mechanisms underlying the various forms of ventricular tachycardias. Programmed electrical stimulation of the heart in humans has, nevertheless, provided new insights into the potential mechanisms of ventricular tachyarrhythmias.[3] More important, the technique has proved of great value in the rational choice of antiarrhythmic agents, conventional and investigational, for controlling sustained ventricular arrhythmias.

Significant advances have also been made in other areas of arrhythmia diagnosis and quantitation. For example, compact Holter analog analysis has been valuable in determining the correlation between the genesis of ventricular arrhythmias and transient or protracted bouts of myocardial ischemia.[4] Furthermore, the role of ambulatory electrocardiographic (ECG) monitoring in the detection and quantitation of complex ventricular ectopy[5] for diagnosis and monitoring treatment of spontaneously occurring ventricular tachyarrhythmias has been substantiated.

Perhaps no less significant is the development of new therapeutic modalities for the control of life-threatening ventricular arrhythmias. First, a plethora of newer antiarrhythmic

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ABBREVIATIONS USED IN TEXT

ECG = electrocardiography
ERP = effective refractory period
PVC = premature ventricular contraction
VT/VF = ventricular tachycardia/ventricular fibrillation

compounds have been synthesized and electrophysiologically characterized and are undergoing clinical evaluation.[6] They hold considerable promise.[7] Second, new surgical techniques aided by electrophysiologic mapping to eradicate the focus of origin or to interrupt reentry circuits of dysrhythmias have been developed and successfully used in certain subsets of patients. Finally, preliminary experience has suggested that mortality in selected patients may be curtailed by using automatic implantable defibrillators, which can identify and terminate ventricular arrhythmias in inpatients[8,9] and outpatients.[10]

In this conference we consider aspects of these various newer approaches to controlling life-threatening ventricular arrhythmias in relation to the fundamental and clinical electrophysiologic mechanisms of such dysrhythmias.

## Cardiac Electrophysiology and the Genesis of Arrhythmias

JAMES N. WEISS, MD:* Regulation of the heartbeat is mediated by the cardiac action potential, a complex phasic electrophysiologic event caused by transient sequential changes in the permeability of the cell membrane to various ions. An action potential arising in the sinus node is transmitted in a highly synchronized manner throughout the myocardium, traversing tissues with heterogeneous electrophysiologic properties, which may change considerably and differently in response to external factors, such as autonomic tone or drugs. To understand the mechanisms that give rise to arrhythmias and how antiarrhythmic drugs may terminate or prevent them, some fundamental features of the cardiac action potential need to be understood.

### The Cardiac Action Potential

Figure 1 shows two fundamental types of cardiac action potentials. The fast response is characterized by a resting membrane potential of -70 mV to -90 mV. When the membrane potential is raised by electrotonic current or spontaneous diastolic depolarization to threshold, a rapid upstroke due to the influx of sodium ions through the fast sodium channel occurs. This upstroke can be blocked by tetrodotoxin. Normal Purkinje fibers show the fast response and may exhibit spontaneous diastolic depolarization, which causes them to fire spontaneously. Normal atrial and ventricular myocardium has the fast response usually without diastolic depolarization. The slow response is characterized by a low resting potential (-40 mV to -60 mV) and a slow action-potential upstroke. The slow upstroke is due to an influx of primarily calcium ions through the slow channel and is blocked by verapamil and other calcium antagonists but not by tetrodotoxin. The slow response can also show diastolic depolarization, such as in the normal sinus node. The atrioventricular nodal cells show the slow response often with diastolic depolarization. Cells normally having a fast response (for example, ventricular myocardium) can develop the slow responses if they are partially depolarized by current, elevated extracellular potassium concentrations, drugs or ischemic damage. The distinction between fast and slow response is important because the action-potential upstroke velocity is a major determinant of conduction velocity in the myocardium. The reduced upstroke velocity due to slow response or attenuated fast response can result in depressed conduction through cardiac tissue, a key predisposing factor to the development of certain types of arrhythmias.

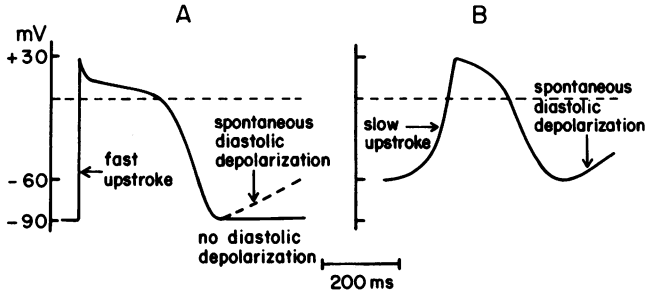


**Figure 1.**—Two types of cardiac action potentials. **A,** The fast response is characterized by a high resting potential and rapid upstroke. Spontaneous diastolic depolarization may occur in Purkinje fibers but not in normal atrial or ventricular myocardium. **B,** The slow response is characterized by a low resting potential and slow upstroke. Spontaneous diastolic depolarization may be present.

Another important concept with respect to arrhythmogenesis and the actions of antiarrhythmic drugs is refractoriness, particularly the indicator designated the *effective refractory period* (ERP). The ERP of cardiac tissue is defined as the period from the onset of the action potential to the time in the cardiac cycle when another action potential that can propagate can be elicited by an applied stimulus. Two types of changes in the ERP should be distinguished. The first is the so-called voltage-dependent change in which the myocardial fiber must repolarize to a certain minimum level of membrane potential before a second propagated action potential can be generated. Thus, shortening of the action-potential will reduce the ERP; the converse will occur with the lengthening of the action-potential duration. Alternatively, the ERP may be lengthened when there is a delay in the return of excitability independently of changes in repolarization (a time-dependent phenomenon). The ERP may outlast the entire duration of repolarization (postrepolarization refractoriness), an electrophysiologic property that is characteristic of slow-channel-dependent fibers, such as the atrioventricular node, and one that may be induced by inhibiting the fast sodium channel—that is, by local anesthetic type of antiarrhythmic drugs—in fast-response-dependent myocardial fibers. The differences between voltage and time-dependent mechanisms of alteration in the ERP (Figure 2) are significant in delineating the fundamental nature of cardiac arrhythmias and in interpreting the action of antiarrhythmic agents.[11]

#### *Genesis of Ventricular Arrhythmias*

The mechanism of ventricular arrhythmias, as in the case of other dysrhythmias, can be categorized into disorders of impulse formation (enhanced automaticity or triggered automaticity), disorders of impulse conduction (such as reentry) or combinations of both.[2] As will be discussed below, these electrophysiologic concepts have been validated reasonably

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TABLE 1.—*Mechanisms of Arrhythmias and Their Probable Clinical Counterparts*

| *Mechanism of Arrhythmias* | *Clinical Arrhythmias* |
|---|---|
| Automaticity | |
| Nontriggered | |
| Normal | Escape rhythm in complete heart block |
| Abnormal | ?Noninducible ventricular tachycardia and supraventricular and ventricular ectopy |
| Oscillatory prepotentials | No clinical counterpart evident |
| Triggered Automaticity | |
| Early afterdepolarizations | ?Ventricular tachycardia due to drug-induced QT prolongation (torsade de pointes) |
| Delayed afterdepolarizations | Ventricular tachycardia due to digitalis toxicity<br>?Mitral valve prolapse arrhythmias |
| Reentry | |
| Ordered reentry | Most inducible ventricular tachycardia, supraventricular tachycardia in Wolff-Parkinson-White syndrome and atrioventricular nodal tachycardia; also probably supraventricular and ventricular ectopy |
| Random reentry | Ventricular fibrillation, atrial fibrillation |
| Reflection | No clinical counterpart apparent |

well in experimental models; their applicability to the clinical context is still essentially inferential[3] but the classification is still of clinical value. For example, clinically there are no electrophysiologic criteria that unequivocally differentiate reentry from the various forms of automaticity, nor are there tools, such as pacemakers, drugs, cardioverters or surgical techniques, that exert specific enough effects to separate the two possibilities. Extracellular recordings of automatic activity, however, hold promise about the possibility of accurate differentiation in the future.[3] Table 1 summarizes the mechanisms of arrhythmogenesis delineated from experimental studies and shows their possible clinical correlates.

*Nontriggered Automaticity*

Arrhythmias due to nontriggered automaticity can result from the normal automaticity, abnormal automaticity or oscillatory prepotentials. The precise basis for such variations of automaticity is still not certain. Normal automaticity refers to diastolic depolarization occurring at high resting potentials (-70 mV to -90 mV) and propagating by a fast response. Abnormal automaticity refers to diastolic depolarization occurring at low resting potentials (-40 mV to -60 mV) and propagating by a slow response. This term may be somewhat misleading because, although this form of automaticity is abnormal for atrial, His-Purkinje and ventricular muscle, it is the normal mechanism of impulse formation in the sinus node. Both normal and abnormal automaticity occur spontaneously and are not dependent on preceding action potentials—that is, they are not inducible by programmed stimulation of the heart.

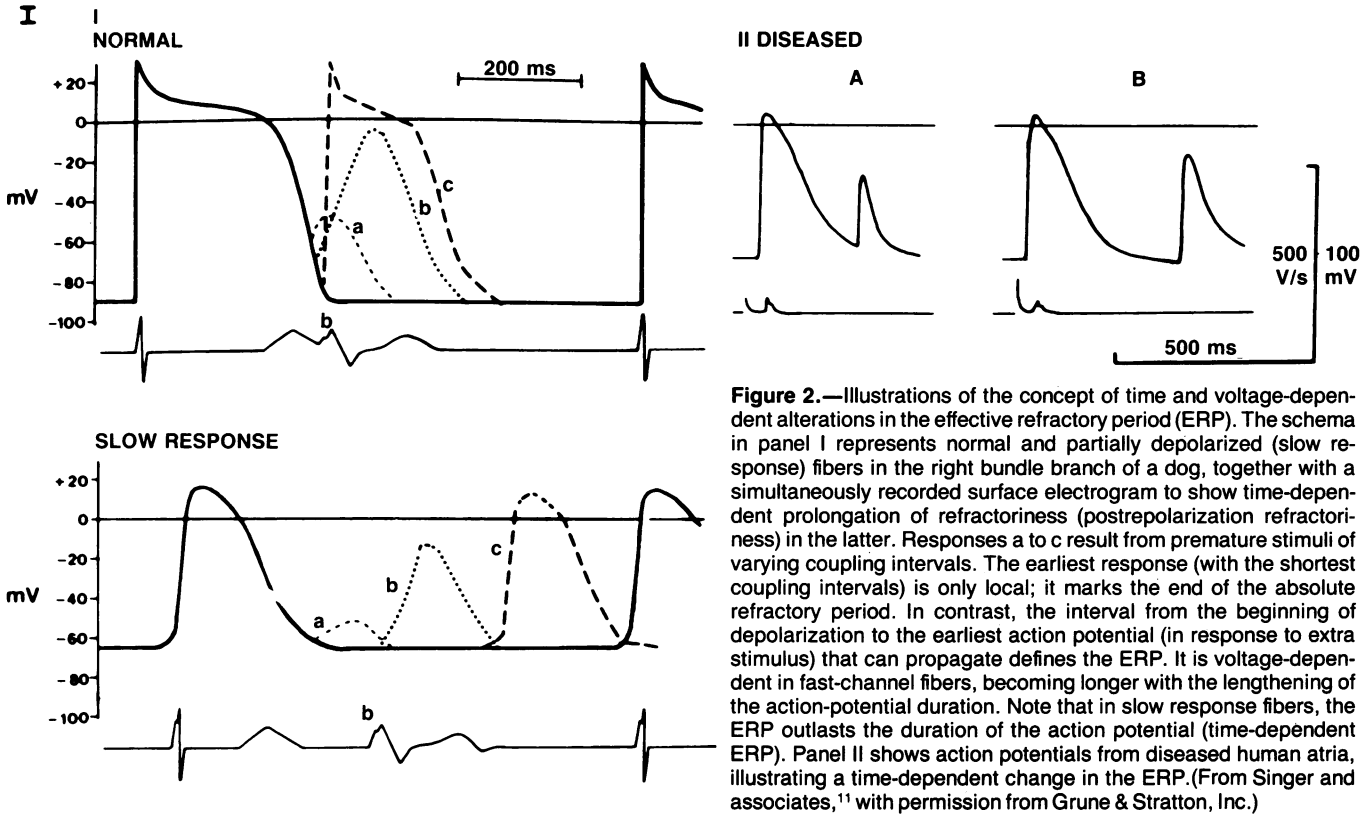


**Figure 2.**—Illustrations of the concept of time and voltage-dependent alterations in the effective refractory period (ERP). The schema in panel I represents normal and partially depolarized (slow response) fibers in the right bundle branch of a dog, together with a simultaneously recorded surface electrogram to show time-dependent prolongation of refractoriness (postrepolarization refractoriness) in the latter. Responses a to c result from premature stimuli of varying coupling intervals. The earliest response (with the shortest coupling intervals) is only local; it marks the end of the absolute refractory period. In contrast, the interval from the beginning of depolarization to the earliest action potential (in response to extra stimulus) that can propagate defines the ERP. It is voltage-dependent in fast-channel fibers, becoming longer with the lengthening of the action-potential duration. Note that in slow response fibers, the ERP outlasts the duration of the action potential (time-dependent ERP). Panel II shows action potentials from diseased human atria, illustrating a time-dependent change in the ERP.(From Singer and associates,[11] with permission from Grune & Stratton, Inc.)

Experimentally, certain techniques may be used to distinguish between these two forms of automaticity.[12] For example, overdrive pacing suppresses normal automaticity but not abnormal automaticity, whereas verapamil suppresses both. Moricizine (ethmozine), an experimental antiarrhythmic drug, more selectively suppresses abnormal automaticity. The role of normal and abnormal automaticity in human ventricular arrhythmias has not been established. Fascicular and idioventricular rhythms in the setting of complete infranodal heart block are examples of normal automaticity, but extremely rapid ventricular arrhythmias probably do not result from this mechanism. Normal automaticity has been seen in diseased human ventricular myocardium.[13] Abnormal automaticity usually occurs in subendocardial Purkinje fibers overlying an area of myocardial infarction in experimental animals[14,15] and in diseased human atrial and ventricular myocardium.[13,16-18] Abnormal automaticity is probably responsible for the high incidence of premature ventricular beats during the first 24 hours after myocardial infarction. In cases of chronic coronary artery disease, abnormal automaticity has been proposed to account for about 10% of patients with recurrent ventricular tachycardia in whom ventricular tachycardia cannot be induced by programmed stimulation of the heart. In patients with noncoronary artery disease, cardiomyopathy and recurrent ventricular tachycardia, the frequency of noninducible ventricular tachycardia is even higher. Parasystole may be the most common clinical manifestation of these forms of automaticity, in which depressed conduction in tissue surrounding the automatic focus protects the focus from being suppressed by sinus impulses (although the sinus impulses may modulate the behavior of the parasystolic focus). This phenomenon has recently been documented to occur in diseased human ventricular myocardium removed during a cardiac procedure.[13] Parasystole may also occur as a result of oscillatory prepotentials reaching the threshold in cardiac fibers (Figure 3), a third form of automaticity[19] whose role in clinical arrhythmias is unknown.

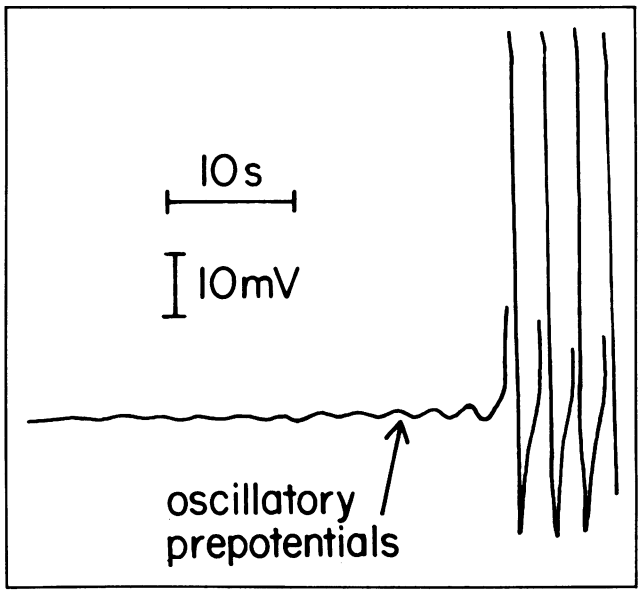


**Figure 3.**—Oscillatory prepotentials. These oscillations in membrane potential may reach their threshold and generate sustained rhythms.

*Triggered Automaticity*

The remaining mechanisms of arrhythmias (triggered automaticity and reentry) have one important common characteristic: they are dependent on preceding stimulation of the heart—that is, they can be induced (and usually terminated) by programmed stimulation of the heart both clinically and experimentally. Initially it was thought that the ability to initiate or terminate an arrhythmia by pacing implied that reentry was the mechanism. Subsequently, however, two forms of automaticity have been recognized that also show this property. Early or delayed afterdepolarizations may occur after a driven action potential (Figure 4). If the afterdepolarization reaches its threshold, it can generate a second action potential and the process may become self-sustaining. Early afterdepolarizations (Figure 4A) occur before the action potential has completely repolarized, generally in cells with a high resting potential. They have been found in Purkinje fibers under conditions of mechanical trauma, severe perturbation of the ionic environment and exposure to toxic concentrations of drugs that severely prolong the action-potential plateau, such as *N*-acetyl procainamide.[19,20] In the latter case, early afterdepolarizations were potentiated by slow pacing rates and suppressed at faster rates. Their role in human ventricular arrhythmias is unclear but it is tempting to speculate that ventricular tachycardia (torsade de pointes) in the setting of a long QT interval—particularly drug-induced—might involve this mechanism, because clinically this arrhythmia is also suppressed by increased heart rates. Delayed afterdepolarizations occur after the driven action potential has fully repolarized and are preceded by an afterhyperpolarization (Figure 4B). Sustained tachycardias from delayed afterdepolarizations can be induced and terminated

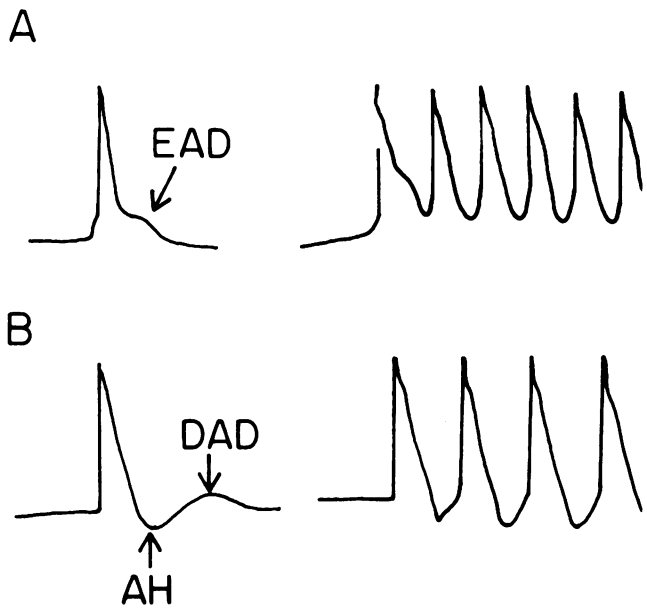


**Figure 4.**—Afterdepolarizations. **A,** Early afterdepolarizations (EAD) occur before repolarization is complete and, if they attain threshold, can produce repetitive activity as shown on the right. **B,** Delayed afterdepolarizations (DAD) occur after the cell has completely repolarized and are preceded by an afterhyperpolarization (AH). If the DAD reaches its threshold, repetitive activity may occur (shown at right).

by premature extrastimuli and are potentiated as the prematurity of the extrastimulus increases.[21] A major feature of this form of automaticity is that overdrive pacing may lead to acceleration of the tachycardia rate followed by termination (overdrive acceleration). Delayed afterdepolarizations can be induced in cells with a high or low resting potential by exposure to catecholamines (in fibers from the coronary sinus, anterior leaflet of the mitral valve and Purkinje system of experimental animals), by severe alterations in the ionic environment or by exposure to toxic concentrations of cardiac glycosides. Depending on how they were induced, delayed afterdepolarizations may be suppressed by verapamil, tetrodotoxin or lidocaine hydrochloride. Recently this form of automaticity has been documented in human myocardium.[13,18] Delayed afterdepolarizations causing repetitive activity were seen in diseased ventricular myocardium surgically removed from patients with recurrent ventricular tachycardia. Similar findings were reported in diseased atrial tissue from a patient with paroxysmal atrial tachycardia.[12,22]

Despite these intriguing correlations, the role of this form of triggered automaticity in human arrhythmias has not been conclusively established. Ventricular arrhythmias in cases of digitalis toxicity are probably due to this mechanism, and it has been postulated that supraventricular arrhythmias associated with the mitral valve prolapse syndrome might result from triggered automaticity in fibers from the mitral leaflet.[23] The phenomenon of overdrive acceleration, believed to be unique to this form of automaticity, is not uncommonly observed in cases of arrhythmia during programmed stimulation of the heart.[24]

*Reentry*

The most common mechanism responsible for human ventricular arrhythmias is reentry (Figure 5A). For reentry to occur, two conditions are necessary: unidirectional conduction block and slow conduction. If two pathways in the heart have disparate refractory periods, then an appropriately timed impulse will conduct through the pathway with the shorter refractory period but fail to conduct through the other pathway (unidirectional conduction block). If conduction through the first pathway is slow enough, the other pathway may have time to regain its excitability and conduct the impulse so that it can reenter the first pathway. The relation between refractoriness and conduction velocity is of critical importance in permitting the impulse to sustain its circus movement. Many antiarrhythmic drugs disturb this relation by altering the electrophysiologic properties that determine refractoriness and conduction velocity. A properly timed external impulse can also terminate the reentrant arrhythmia by simultaneously blocking both pathways of the circuit (Figure 5). These principles form the basis for studying clinical arrhythmias during a cardiac electrophysiologic study (see below). The slow response action potential (Figure 1B), or an attenuated fast response potential with slow conduction, may predispose ventricular myocardium to the development of reentry. The slow response has been documented to occur in diseased human ventricular tissue surgically removed from patients with recurrent ventricular tachycardia.[13,18] Recently it has been shown that under certain conditions the fast response can also be associated with slow conduction predisposing to reentry.[25]

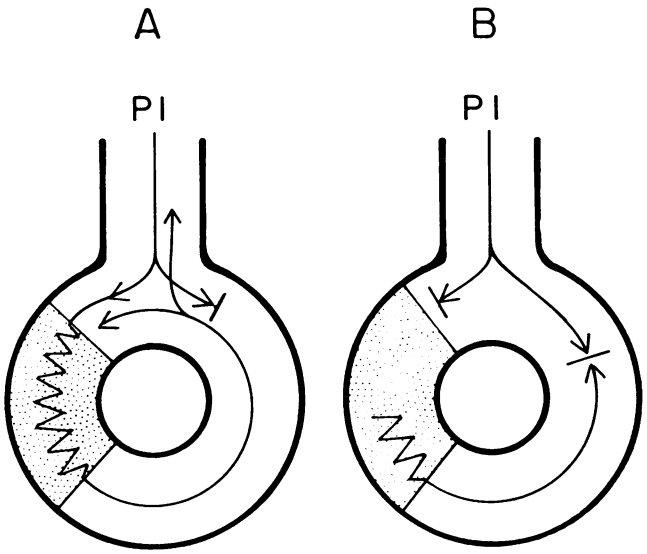


**Figure 5.**—Schema of reentry. **A,** Conduction of a premature impulse (PI) is blocked in one direction but conducts slowly (indicated by sawtoothed line) in the other. The slow conduction through one pathway permits the other pathway to regain excitability so that the impulse can reenter the loop. **B,** Termination of reentry by a premature impulse. The PI arrives too early to be conducted through the slow region (stippled area) and collides with the reentry impulse in the other pathway.

In experimental studies three major types of reentry have been described:

1. *Ordered reentry* occurs when the anatomic pathway of the reentrant circuit is relatively fixed. The classic example of ordered reentry in human arrhythmia where the reentrant circuit is well defined is circus-movement tachycardia in cases of the Wolff-Parkinson-White syndrome. Except for bundle branch reentry,[2] in which at least part of the reentrant circuit may be defined, the reentry circuits in ventricular tachycardia are difficult to establish with certainty. Most cases of recurrent ventricular tachycardia (in which the QRS morphology is unchanging) have been assumed to be due to ordered reentry in a diseased portion of the ventricular myocardium. Two lines of evidence tend to support this. First, most recurrent ventricular tachycardia can be initiated and terminated by programmed stimulation of the heart, which excludes nontriggered automaticity as the mechanism. Second, in several patients with recurrent ventricular tachycardia, intracardiac recordings have detected continuous electrical activity at sites believed to be near the origin of the tachycardia, which is present during tachycardia but not during sinus rhythm (Figure 6).[26] The intracardiac electrode detects electrical activity from many cells within a certain distance of its tip. If the total reentry circuit is located within this distance, electrical activity would be continuously detected throughout systole and diastole by the electrode during tachycardia but not during sinus rhythm. Because of artifacts, other investigators have questioned the reliability of this finding.[27]

2. *Random reentry* occurs when the anatomic pathway of the reentering impulse constantly shifts. It is characterized by an impulse that chaotically turns in and out on itself, its path

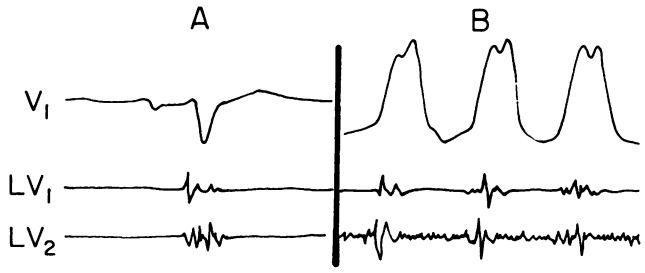


**Figure 6.**—Continuous electrical activity during ventricular tachycardia (VT). Electrocardiographic lead $V_1$ and two intracardiac leads positioned in the left ventricle ($LV_1$ and $LV_2$) are shown. **A,** During sinus rhythm, no electrical activity is detected at either intracardiac site during diastole. **B,** During VT continuous electrical activity is detected throughout systole and diastole at site 2, but not site 1, indicating that site 2 is near the reentry circuit causing VT.

being determined by constantly shifting boundaries of refractory tissues. Atrial and ventricular fibrillations are thought to be examples of random reentry. Unlike ordered reentry, random reentry can be induced in completely normal myocardium by extremely rapid pacing or delivering critically timed extrastimuli at high currents. A critical minimum mass of tissue is necessary to induce fibrillation in most myocardial tissue, supporting the hypothesis that fibrillation is due to reentry. In aggregates of cultured myocytes, however, electrical activity resembling fibrillation has been due to automaticity.[28]

3. *Reflection* differs from the other types of reentry in that only a single pathway is necessary to generate reentry. Figure 7 shows that if a strip of myocardium has a depressed segment, an impulse entering this segment may conduct slowly enough so that by the time it reaches normal tissue again (at A), the normal tissue at B has regained excitability. If excitation at A causes an electrotonic depolarization at B large enough to reach its threshold, a "reflected" action potential is generated. Reflection can be shown in Purkinje fibers and ventricular myocardium by artificially depressing a central

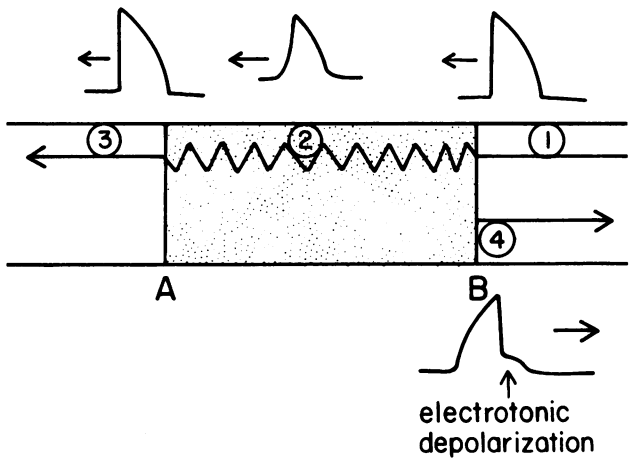


**Figure 7.**—Reflection. In a strip of cardiac tissue with a central zone (AB) of depressed conduction, an impulse (1) reaching point B is conducted slowly through the depressed area (2) and emerges at point A (3). Excitation at point A causes electrotonic current at point B to raise the local membrane potential to threshold and stimulate a "reflected" action potential (4). Representative action potentials are shown for each step 1 through 4.

segment of tissue[29]; whether or not reflection contributes to clinical arrhythmia has not been established.

In the preceding discussion the major mechanisms of tachyarrhythmia have been described. These have been identified in experimental studies and are believed to account for the common human arrhythmias observed clinically. In many cases specific clinical arrhythmias cannot yet be definitely attributed to a single mechanism. Through our expanding knowledge of the basic electrophysiology of arrhythmias, an increasingly rational approach to the treatment of these disorders using drugs, pacing techniques and surgical intervention can be devised.

## Electrophysiologic Mechanisms of Antiarrhythmic Drugs

DR. SINGH: For the control of malignant ventricular arrhythmias, the pharmacologic approach still has the widest appeal, applicability and scope, despite the fact that a single ideal antiarrhythmic agent remains to be developed. For the rational pharmacologic basis for the treatment of arrhythmias to be established, not only does the nature of cardiac arrhythmia need to be understood, but also the fundamental mechanism of action of antiarrhythmic agents needs to be defined. In this regard, conventional and newer compounds can now be divided electrophysiologically into four discrete classes[30,31] on the basis of whether they inhibit the fast response in cardiac muscle (I), decrease sympathetic excitation to the heart (II), homogeneously lengthen cardiac repolarization without altering depolarization (III) and inhibit or abolish the slow response (IV). The major compounds in various classes and subclasses of action are listed in Table 2.

Class I drugs depress the fast sodium current (fast response) in cardiac muscle, thereby lengthening the dependent effective refractory period; the resting membrane potential is unaffected but phase 4 is depressed while the effect on repolarization is variable. For example, in the case of some drugs (now designated as class IA, such as quinidine, procainamide hydrochloride and disopyramide phosphate) the pronounced reduction in the fast response (or the fast sodium current) is associated (in an independent way) with a modest lengthening of the action potential (or QTc interval), a property that may be both beneficial and deleterious under different conditions. For example, in atrial flutter and fibrillation, lengthening of the atrial action potential by these agents may contribute to their tendency to restore and maintain sinus rhythm. In ventricular myocardium the lengthening of the QTc interval in conjunction with a greatly reduced conduction velocity may give rise to atypical ventricular tachycardia (torsade de pointes) in excessive doses or when associated with hypokalemia or hypomagnesemia. In the case of some class I agents, the duration of the action potential may actually become shorter. With these agents (designated as class IB and typified by lidocaine, mexiletine, tocainide, phenytoin, aprindine hydrochloride and possibly propafenone, pirmenol hydrochloride and moricizine), the net effect on the ERP is a balance between the time-dependent increase due to the inhibition of the fast channel and the *decrease* due to abbreviation of the time course of repolarization. Recently, another discrete subcategory (designated IC) of class I agents has become available;

TABLE 2.—*Comparative Mechanisms of Action of Antiarrhythmic Agents*

| *Class I* | *Class II* | *Class III* | *Class IV* |
|---|---|---|---|
| A. Quinidine<br>Procainamide hydrochloride<br>Disopyramide phosphate | A. Propranolol hydrochloride<br>Oxprenolol hydrochloride<br>Alprenolol hydrochloride<br>Pindolol<br>Timolol maleate<br>Nadolol<br>Acebutolol<br>Atenolol | Sotalol hydrochloride*<br>Amiodarone<br>Bretylium tosylate<br>Clofilium phosphate<br>*N*-Acetyl procainamide<br>Melperone | A. Verapamil<br>Diltiazem hydrochloride<br>(Nifedipine)†<br>Tiapamil<br>Gallopamil (D-600) |
| B. Lidocaine hydrochloride<br>Mexiletine<br>Tocainide<br>Aprindine hydrochloride<br>Moricizine (ethmozine)<br>Phenytoin<br>Propafenone<br>Pirmenol hydrochloride | B. Sotalol* | | B. Bepridil hydrochloride |
| C. Flecainide acetate<br>Encainide hydrochloride<br>Cibenzoline<br>Indecainide<br>Lorcainide hydrochloride | | | |

*Sotalol differs from other β-antagonists in lengthening cardiac repolarization. Also note that bepridil is a calcium-antagonist that differs from other members of the class in depressing fast channel activity.

†Nifedipine has no direct antiarrhythmic actions.

these agents greatly depress conduction in all parts of the heart, and some of them also have a potent suppressant action on premature ventricular contractions ("PVC killers"). The most prominent compounds in this category are flecainide acetate, encainide hydrochloride (and its metabolites), lorcainide hydrochloride and cibenzoline. Another feature that these compounds share is the differential effect that they have on repolarization in ventricular muscle and in Purkinje fibers, lengthening it in the former and shortening it in the latter. Significant arrhythmogenic potential of some of these compounds may relate not only to their pronounced depressant effect on conduction but also on the disparity in their actions on cardiac repolarization providing the substrate for focal re-excitation.

Some general features of class I agents relative to their value in controlling ventricular tachyarrhythmias should be emphasized. Because these drugs lengthen the ERP and depress the tendency to spontaneous depolarization, they have a wide spectrum of antiarrhythmic action, being effective in arrhythmias due to reentry and in those caused by enhanced automaticity. A feature of class I agents, which has also emerged recently from clinical studies, is that, as a class, the long-term efficacy of these compounds in controlling ventricular tachyarrhythmias may be predictable on the basis of their ability to prevent the reinduction of ventricular arrhythmias by programmed electrical stimulation of the heart in a clinical electrophysiology laboratory.[32] These observations suggest that these compounds alter the substrates required for reentry in patients with organic cardiac disease.

The class II agents, particularly the β-adrenoceptor-blocking drugs, reduce sympathetic excitation of the heart. The antiarrhythmic spectrum of these drugs is virtually identical despite the somewhat varying pharmacologic properties in terms of their potencies as local anesthetics, as partial agonists and as cardioselective or nonselective agents.[34] Their only electrophysiologic action of clinical relevance is the fact that all block phase 4 depolarization, especially that augmented by endogenous or exogenous catecholamines. We[33] have shown that the overall antiarrhythmic spectrum of action of β-blockers in cases of chronic ventricular arrhythmia will be narrow. Indeed, the agents in this class have a low potency for suppressing premature ventricular contractions[34] and rarely are they prophylactically effective against life-threatening ventricular tachyarrhythmias.[35] There are, however, two exceptions: First, this class of agents is particularly effective in exercise-induced ventricular tachycardia that is thought to be due to triggered automaticity.[36] Second, β-blockade is the pharmacologic therapy of choice in the relatively rare syndrome of long QT interval with a propensity to recurrent ventricular tachycardia or fibrillation, an arrhythmia and ECG abnormality most likely due to asymmetric sympathetic stimulation of the heart.[37] As a class of cardioactive agents, however, β-blocking compounds have recently drawn much attention because of their propensity to reduce the incidence of sudden death in survivors of acute myocardial infarction.[38] This effect is related to the β-blocking property of the compounds and seems to be mediated indirectly through amelioration of ischemia rather than a primary antiarrhythmic action.[39]

Perhaps one of the most significant observations in the past

ten years in the characterization of antiarrhythmic mechanisms has been that the uniform lengthening of the action-potential duration has a potent effect in preventing the development of arrhythmia.[6,40,41] This has been suggested by the alterations in the duration of repolarization of intracellularly recorded action potentials in hyperthyroid and hypothyroid atria.[42,43] It is also indicated by the striking effect of the drug amiodarone in prolonging the absolute refractory period in cardiac muscle[41] with little effect on the upstroke velocity of phase 0 of the transmembrane action potential (see below). This effect is also shown by bretylium tosylate during administration for an acute condition, myocardial ischemia,[6] and by amiodarone after protracted therapy.[41] Such an effect has been considered to be a distinct mechanism (class III) for terminating resistant ventricular arrhythmias. Several agents that seem to act predominantly by lengthening the action-potential duration (with the consequent prolongation of the ERP) are currently under study: sotalol hydrochloride, amiodarone, clofilium phosphate and *N*-acetyl procainamide. Other compounds that may also show, at least in part, the so-called class III activity are bepridil hydrochloride[44] and melperone.[45] Recent evidence shows that certain class III agents—such as amiodarone and sotalol—while being broad-spectrum antiarrhythmic compounds, may emerge as the most significant agents for the control of life-threatening ventricular arrhythmias. They seem to be effective in arrhythmias due to reentry and enhanced automaticity. However, their role in ventricular arrhythmias due to triggered automaticity—exercise-induced or torsade de pointes—is not defined. One feature of the action of these compounds as a class merits emphasis: because of their selective effect on myocardial repolarization, they exert no intrinsic negative inotropic effect[46] and some may be frankly positively inotropic.[45] Thus, unlike other electrophysiologic classes of antiarrhythmic compounds, class III agents exert little or no myocardial depressant effect, even in patients with cardiac failure. They constitute, therefore, a significant advance in the control of life-threatening ventricular tachyarrhythmias because most of these occur in patients with severe cardiac disease.[47]

Finally, agents that selectively block the slow channel in the myocardium have been categorized as showing a class IV antiarrhythmic action.[31] Verapamil is a prototype; it has little effect on the upstroke velocity of phase 0: it accelerates phases 1 and 2 of repolarization and depresses phase 4, especially where it is slow-channel dependent (slow response). In humans, calcium antagonists have no significant effect on the effective refractory period of the ventricle or the His-Purkinje system. Thus, it is not surprising that these compounds as a class exert little or no direct antiarrhythmic effects in cases of ventricular tachyarrhythmia,[48] nor do they predictably suppress premature ventricular contractions in patients with cardiac disease.[49] On the other hand, calcium antagonists may exert a potent antiarrhythmic effect indirectly by controlling myocardial ischemia complicating coronary artery spasm[50] and may become prophylactic agents of choice in this particular context.[51]

Thus, in the prophylactic control of most malignant or life-threatening ventricular arrhythmias, neither β-blockers nor calcium antagonists have a major role. In the past, class I agents have dominated the pharmacologic therapy for such tachyarrhythmias. Recent studies,[50-55] especially with the drug amiodarone, have shown the role of class III agents to emerge as an effective alternative and the possibility that the judicious use of this category of compounds may make a significant inroad into the morbidity and mortality figures from life-threatening ventricular arrhythmias in patients with cardiac disease. Thus, a critical reappraisal of the role of various electrophysiologic classes of antiarrhythmic compounds in the prophylactic control of life-threatening ventricular tachyarrhythmias is timely.

## Drug Therapy for Ventricular Arrhythmias

KOONLAWEE NADEMANEE, MD:* Pharmacologic suppression remains the mainstay of therapy for ventricular tachyarrhythmias,[1-6] despite recent advances in surgical techniques and implantable antitachycardia and antifibrillatory devices (see below). The pharmacologic approach is applicable to the entire spectrum of ventricular tachyarrhythmias from simple or complex premature ventricular contractions (PVCs) to ventricular fibrillation. Although the data are not conclusive, increasing evidence has tended to delineate those subsets of patients with ventricular tachyarrhythmias who need aggressive antiarrhythmic therapy. Recent reports[56-58] have clearly established the benign nature of ventricular tachyarrhythmias in patients with structurally normal hearts. Unless patients are severely symptomatic, no specific antiarrhythmic therapy in such patients is either indicated or justified. In contrast, patients having structural heart disease (especially coronary artery disease) with ventricular tachyarrhythmias can be categorized into somewhat overlapping subsets in all of whom successful therapy might reasonably be expected to enhance survival; the presence of ventricular dysrhythmias, symptomatic or nonsymptomatic, in such patients is associated with sudden arrhythmic deaths. These arrhythmias are, therefore, designated life-threatening or malignant and patients with such dysrhythmias are recognized to be at high risk for sudden death.[56,59-64] Three categories of patients are recognized. The first includes those patients with frequent and complex PVCs without sustained ventricular tachycardia. The second comprises patients with symptomatic or nonsymptomatic ventricular tachycardia without a history of previous cardiac arrest, and the final group consists of the survivors of out-of-hospital cardiac arrests due to ventricular tachycardia or fibrillation. These three groups of patients constitute a continuum representing a spectrum of severity in electrical instability of the myocardium.

### *Significance of Premature Ventricular Contractions in Patients With Cardiac Disease*

There is strong evidence fortified by recent data from ambulatory ECG monitoring that in patients with cardiac disease (especially coronary artery disease), the frequency and complexity of PVCs constitute indicators of increased risk of sudden cardiac death.[56,59-61] The evidence is particularly compelling in patients with reduced ventricular function.[59] For example, Schulze and colleagues[65] found that although advanced grades of PVCs occurred essentially in those with left ventricular ejection fractions of less than 40%, sudden arrhythmic deaths occurred only in patients who also had advanced grades of PVCs. Moreover, Rub-

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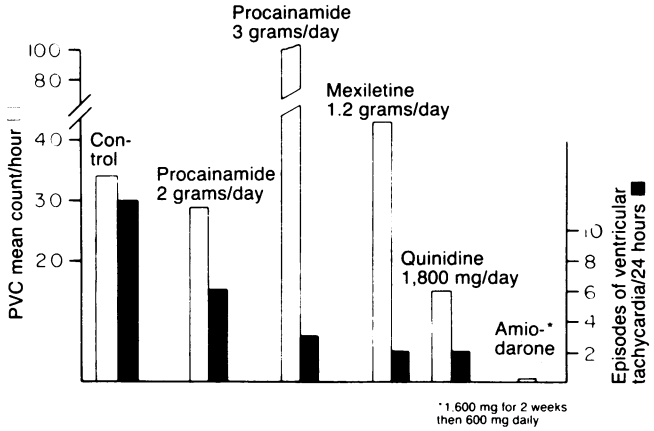


**Figure 8.**— Effect of various antiarrhythmic agents on total premature ventricular contraction (PVC) counts (ordinate on the left) and ventricular tachycardia beats (ordinate on the right) computed from 24-hour ambulatory electrocardiographic recordings. The goal of therapy is to eliminate ventricular tachycardia beats and, if possible, to reduce total PVC counts by more than 90%. In this patient, this goal was met only with the use of amiodarone (K. Nademanee, MD, and B. N. Singh, MD, PhD, unpublished observations, March 1982).

erman and associates[61] noted that patients with congestive heart failure who did not have advanced grades of PVCs showed a lower propensity for sudden cardiac death than those who had such arrhythmias but never had cardiac failure. These data provide a clear rationale for the pharmacologic suppression of advanced grades of PVCs in patients with cardiac disease and compromised ventricular function even in asymptomatic patients. To date, however, no systematic trial with antiarrhythmic compounds has unequivocally shown that either suppressing the total number of PVCs (by whatever percentage) or eliminating their complexity leads to enhanced survival in this subset of patients. Nevertheless, because of the established risk of sudden death due to PVCs and because of inferential evidence from patients with sustained (see below) ventricular tachycardia in whom eliminating advanced PVCs seems to prolong survival,[56] we feel aggressive attempts at eliminating complex PVCs and nonsustained runs of ventricular tachycardia are justified. Our approach is exemplified in Figure 8. The arrhythmias are verified and quantitated under control conditions by multiple ambulatory ECG recordings and serially on incremental dosing regimens of antiarrhythmic compounds under serum drug concentration control until the goal of therapy (without the development of side effects) has been met. As emphasized above, β-blockers and calcium antagonists have a low order of potency to suppress PVCs.

The precise potency profile for all conventional and investigational antiarrhythmic compounds is not available but the introduction of newer class I agents, such as encainide[66] and flecainide,[67] and class III agents such as amiodarone[68] indicates that not only a predictable PVC suppression may be attained by these agents but long-term controlled observations may permit the evaluation of prognostic significance of the PVCs. In a recent double-blind multicenter study[69] involving 280 patients with classic PVCs, 85% of patients given flecainide had 80% suppression of PVCs versus 57% of patients achieving the same suppression by quinidine. Furthermore, in 68% of patients flecainide produced a complete suppression of couplets and beats of ventricular tachycardia, whereas only 33% of the patients treated with quinidine had complete suppression. Figures for encainide are probably similar.[66] Although similar figures for procainamide and disopyramide are not available in this regard, they are unlikely to be different from those for quinidine. Our studies[68] and those of others[70] have shown that the drug amiodarone has the potency to reduce total PVC counts by more than 90% and to eliminate couplets and runs of ventricular tachycardia in more than 80% to 90% of all patients. Thus, antiarrhythmic compounds with a range of potency to suppress PVCs are now becoming available. For this reason, it is clearly important to establish by stringently controlled clinical trials whether PVC suppression is attended by a reduced incidence of sudden death in patients with cardiac disease.

### *Sustained Ventricular Tachycardia and Recurrent Cardiac Arrests*

The subsets of patients with these two types of manifestations of ventricular tachyarrhythmias clearly represent those with the highest possible risk for sudden death. Such patients are in the greatest need of aggressive medical therapy; they also provide the widest scope and challenge for reducing mortality rates by the prophylactic control of recurrent arrhythmias. It is in these two subsets of patients that the use of all the newer modalities of treatment, such as investigational antiarrhythmic drugs,[66,71] surgical treatment of arrhythmias[72] and implantable electronic devices,[8-10] may lead to improved prognosis. Between 1930 and 1960, the six-month mortality in patients with ventricular tachycardia was between 50% and 80%, the mortality correlating with the severity of the underlying disease. A recent report from Stanford indicates an actuarial six-month mortality rate of 18 ± 3%.[73] Other studies, especially with survivors of out-of-hospital cardiac arrests, have shown a mortality figure between 30% and 50% in the first year.[60-64] Aggressive prophylactic therapy for such patients is clearly imperative. An appreciation of the clinical features of both subsets of these patients is relevant to the pharmacologic strategies necessary for the control of their ventricular tachyarrhythmias. In a variable number of patients with ventricular tachycardias and sudden death syndrome, a reversible cause can be identified and dealt with. This may range from electrolyte disturbances, arrhythmogenic drugs (including many antiarrhythmic compounds), episodic myocardial ischemia—such as that due to coronary artery spasm—to specific clinical situations in which a particular mode of therapy may be highly efficacious—such as β-blockade or left stellate ganglionectomy for the congenital long QTc-interval syndrome.[74] In most patients, however, the underlying cardiac disease is not reversible and continues to provide the substrate for reentry and enhanced automaticity[73]; the left ventricular ejection fraction is reduced,[68] often severely.[52]

From the standpoint of pharmacologic therapy, two features are worthy of emphasis. In survivors of sudden arrhythmic arrests, about 80% to 90% show frequent and often complex PVCs in serial 24-hour ambulatory ECG records[52,75]; in about 70% to 80% ventricular tachycardia or fibrillation is reproducibly inducible by programmed electrical stimulation of the heart.[52,76] In patients with symptom-

atic sustained ventricular tachycardia, PVCs are also present in about 80% to 90%,[68] whereas inducible ventricular tachycardia/ventricular fibrillation (VT/VF) may be elicitable in the 90% of patients.[32,73,77,78] Thus, in only a small fraction of patients, ambulatory ECG monitoring and programmed electrical stimulation fail to document the presence of electrical instability of the myocardium. These observations have therefore provided the basis for developing antiarrhythmic drug therapy for life-threatening ventricular arrhythmias.

*Selection of Antiarrhythmic Drugs: Suppression of Spontaneous Versus Inducible VT/VF as Prognostic Indices*

In selecting effective drug regimens for the control of life-threatening ventricular arrhythmias, three discrete approaches have been promulgated. The first was suggested by the work of Myerburg and co-workers,[75,79] who reported that procainamide or quinidine, given in doses to achieve and maintain therapeutic plasma concentrations, prevented VT/VF in all six patients, whereas VT/VF recurred in eight of ten patients in whom plasma drug concentrations were unstable and generally below the therapeutic range. Their data showed a dissociation between the suppression of PVCs and prevention of VT/VF and suggested the maintenance of the so-called therapeutic plasma drug values as a means to avert recurrent cardiac arrest. However, the number of patients in this study was small, the pretreatment analysis of arrhythmias was lacking and there was no control group. The second approach is the one indicated by the data reported by Graboys and colleagues.[56] They showed that eliminating complex ventricular ectopy (Lown, grades 4 and 5) by antiarrhythmic agents in patients with malignant ventricular arrhythmias (including those surviving cardiac arrest) led to a reduction in the incidence of sudden death. For example, of 123 such patients treated by individualized antiarrhythmic drug regimens and studied for 29.6 months, 35 patients died (11.2% annual mortality), of whom 23 died suddenly (8.2% annual mortality). Among 98 of these patients in whom antiarrhythmic drugs eliminated advanced grades of PVCs, only six deaths occurred (an annual death rate of 2.3%). In contrast, of the 25 patients in whom advanced PVCs were not controlled, 17 died. Various antiarrhythmic agents were used in the study and the most significant determinant of prognosis was simply the suppression of complex ventricular ectopy.

Finally, the method of drug selection that has attracted most attention recently is one in which the suppression of inducible VT/VF during acute drug testing has been found to predict the long-term outcome during long-term prophylactic therapy.[32,78,80] Numerous investigators have found that if VT/VF induced by programmed electrical stimulation can be suppressed by antiarrhythmic compounds at drug concentrations that subsequently can be attained during prolonged oral therapy using class I agents,[32,78,80] long-term arrhythmia control is highly predictable. Conversely, it has been found that the inability to identify an effective drug regimen during programmed electrical stimulation is predictive of a poor clinical outcome,[32,73,81] again when class I agents are used. The technique is clearly promising but it is not universally applicable, nor has it been fully validated or proved unequivocally reliable. For example, of the 31 patients reported by Ruskin and associates[81] to survive sudden out-of-hospital cardiac arrest, VT/VF was not inducible in six of the patients. In six others, acute drug testing failed to identify an effective regimen—that is, in about 40% the technique was not helpful. In the remaining 19 patients treated (9 with mexiletine only, 5 with quinidine only, 2 with a combination regimen, 3 with amiodarone) on the basis of the suppression of inducible VT/VF, there were no deaths during a mean follow-up of 15 months. Morady and associates, however, in a study of 45 patients who died suddenly,[76] found inducible ventricular tachycardia in 34 patients (76%); drug testing using conventional (class I) drugs showed suppression of inducible ventricular tachycardia in 9 of 34 patients (26%). Three of these nine patients (33%) had recurrent ventricular tachycardia or sudden death during a mean follow-up period of 20 months while receiving long-term therapy instituted on the basis of the induction studies.

The reasons for the differences between the data reported by Ruskin and co-workers[81] and those by Morady and associates[76] are not certain but they emphasize the need for further critical evaluation of the technique of invasive electrophysiologic studies in this regard before it can be promulgated unreservedly as a reliable method for the design of ongoing antiarrhythmic therapy in patients with malignant ventricular tachyarrhythmias. Furthermore, although the method is here to stay, at present it is not entirely certain whether it is indeed superior to that involving the suppression of spontaneously occurring ventricular arrhythmias documented on ambulatory ECG recordings. A stringently controlled study comparing the clinical utility of both techniques *in the same study* is still wanting. Furthermore, the two approaches are *not* mutually exclusive and, though the invasive nature of programmed electrical stimulation cannot be ignored, it is of much value not only for establishing the precise diagnosis of a wide QRS-complex tachycardia but also for establishing the appropriate therapy when other methods may not be applicable. Electrode catheter arrhythmia induction is, of course, an integral adjunctive resource for surgical treatment of arrhythmia.

*Control of VT/VF by Lengthening Cardiac Repolarization*

As indicated above, the so-called class III action is typified by the properties of the drug amiodarone, the best studied compound in this regard.[52-55] The compound also has a remarkable potency[68] for suppressing PVCs in a predictable manner.[52] To test the significance of PVC suppression versus inhibition of inducible VT/VF by programmed electrical stimulation, we have systematically (but not by blinded protocol) evaluated the drug's effect using optimal dosage schedules[52,68] in two independent series of patients. In the first,[68] 96 patients with life-threatening ventricular arrhythmias *refractory to two or more conventional agents* were treated with amiodarone and studied for 6 to 40 months (mean, 15 months). At the time of analysis, 75 patients were alive and well, with 7 patients dying from nonarrhythmic causes and 5 from arrhythmias. Nonfatal arrhythmias recurred in four patients, one early and three with late onset, and intolerable side effects occurred in five patients. In 72 of 96 patients, 24-hour Holter recordings were done before amiodarone therapy was administered; 63 (87.5%) showed frequent PVCs with complex forms and runs of ventricular tachycardia while not re-

ceiving specific antiarrhythmic therapy. The effects of amiodarone, documented by serial Holter recordings, are shown in Figure 9. Amiodarone, after the initial loading dose and at different periods of maintenance therapy, eliminated runs of ventricular tachycardia and reduced the total of premature ventricular contractions by 90% or more in 59 (93.7%) of 63 patients. In 43 such patients, arrhythmia induction by programmed electrical stimulation could be undertaken before and in 30 patients during steady-state drug therapy. In 14 of 30 patients VT/VF could still be reinduced by programmed electrical stimulation during drug therapy despite excellent clinical results. Indeed, with respect to the clinical outcome, the degree of suppression of spontaneously occurring arrhythmias found on Holter recordings and the magnitude of the increase in the ventricular ERP, the subset of 14 patients in whom VT/VF was reinducible during amiodarone therapy was indistinguishable from that of the 16 patients in whom it was not reinduced by programmed electrical stimulation during drug therapy despite excellent clinical results.

The results of these studies were concordant with our data in 40 consecutive patients surviving out-of-hospital cardiac arrests, and in whom conventional drugs were either not effective or not tolerated.[52] The mean ejection fraction for the group was $0.29 \pm 0.12$. The flow diagram in Figure 10 shows the clinical outcome of the 40 patients treated prophylactically with amiodarone. During the long-term administration of therapy the recurrence rate was low. This is further corroborated by determining the influence of amiodarone on the occurrence of VT/VF and survival analyzed by the life-table method. In 22 patients, data with respect to recurrent VT/VF before amiodarone therapy and during continuous amiodarone treatment were available. Figure 11 shows such an analysis for the significance of the difference of the occurrence of VT/VF during a 15-month period of observation. A significant difference ($P < .0005$) was found between the frequency of the recurrence of arrhythmias before and during amiodarone therapy. In Figure 12 the percentage of patients who remained free of VT/VF while taking amiodarone (upper panel) is presented. The recurrence rate of VT/VF and the total mortality (including four deaths not from arrhythmia) was low during the 24-month period of observation. The total annual mortality was less than 10%; the arrhythmic mortality was less than 5%, a figure that is concordant with data from another recent study.[76] In this study, however, the outcome was not studied relative to the suppression of spontaneous versus inducible VT/VF.

In 34 of our 40 patients, 24-hour Holter recordings could be done while all antiarrhythmic therapy was discontinued and before the amiodarone regimen was started. In all, 29 patients (85%) showed frequent runs of PVCs and one or more episodes of ventricular tachycardia—three or more consecutive runs of PVCs at a rate of more than 100 beats a minute. In five patients there were no runs of ventricular tachycardia beats. In all 29 patients in whom control 24-hour Holter recordings

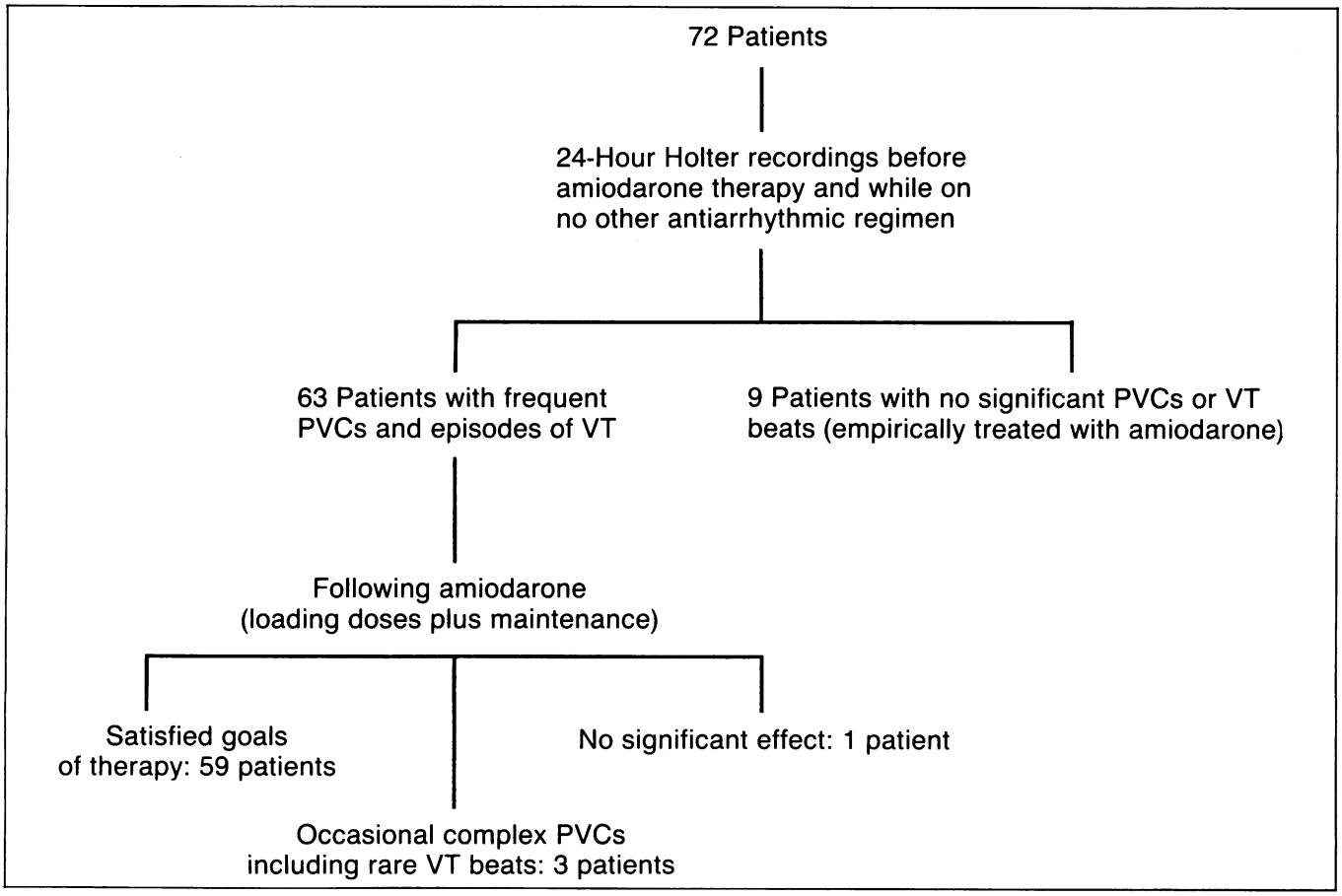


**Figure 9.**—The effects of long-term amiodarone therapy, showing the frequency of occurrence of premature ventricular contractions (PVCs) and ventricular tachycardia (VT) in patients with symptomatic and nonsymptomatic recurrent ventricular tachycardia and cardiac arrest. (From Nademanee et al,[68] with the permission of the authors and *Annals of Internal Medicine.)*

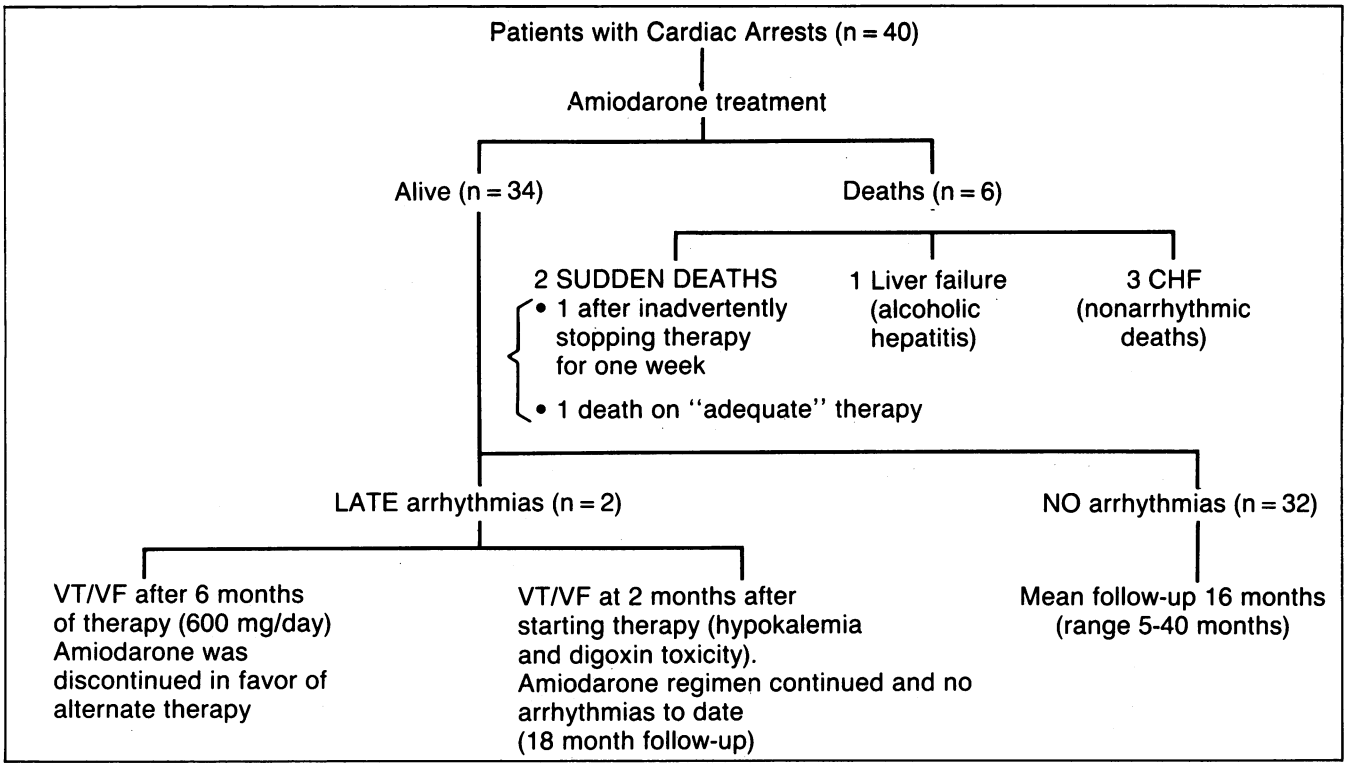


**Figure 10.**—Flow diagram showing the clinical outcome in 40 survivors of sudden cardiac arrests treated prophylactically with amiodarone with initial loading doses and subsequent maintenance doses of the drug. Note the low recurrence rate of arrhythmias during long-term therapy. (From Nademanee et al,[52] with the permission of the authors and the *American Heart Journal.*) CHF = congestive heart failure; VT/VF = ventricular tachycardia/ventricular fibrillation.

were available, the use of amiodarone eliminated ventricular tachycardia beats and reduced the total PVC counts by 90% to 95% during long-term steady-state drug administration. Subsequent serial Holter monitoring showed recordings free of ventricular tachycardia beats with a low rate of PVC occurrence.

Of the 40 patients, 27 underwent electrophysiologic studies. In 21 patients (78%) ventricular tachycardia (in 14 sustained, in 7 unsustained) was reproducibly inducible by programmed electrical stimulation and in 6 patients it was not. Of the 21 patients with inducible ventricular tachycardia, 4 did not consent to the procedure during amiodarone therapy. Of the remainder, ventricular tachycardia reinduction was possible in 11 patients (65%). Despite this high rate of reinduction on a regimen of amiodarone, suppression of complex ventricular ectopy and runs of ventricular tachycardia on 24-hour ambulatory recordings were invariable. Similarly, a salutary clinical outcome was not compromised by the inducibility of ventricular tachycardia during long-term amiodarone therapy.

Our data on the use of amiodarone, with rare exceptions,[82] are consistent with the recent findings of the other investigators[55,83] and permit several conclusions. First, when the drug is used as a single agent in an appropriate dosage regimen, it is extremely effective in controlling life-threatening ventricular tachyarrhythmias, with low incidence of limiting side effects.[68,83,84] Second, in patients in whom an arrhythmia does recur, it is not predictable on the basis of the lack of suppression of inducible VT/VF; the converse also seems to hold, inasmuch as clinical occurrences of ventricular tachycardia were occasionally seen despite the complete suppression by the drug of inducible VT/VF. Third, the drug seems to be extraordinarily potent in suppressing complex ventricular ectopy and total ectopic activity in most patients taking amiodarone over protracted periods. This is in line with the comparable degree of a suppressant effect on ventricular ectopy noted by McKenna[70] in patients with hypertrophic cardiomyopathies who were given amiodarone. Finally, inasmuch as most patients in our series had a near total suppression of ventricular ectopy, and recurrences of clinical VT/VF were not seen, a positive correlation between the two indexes is suggested. Whether there is a causal relation between them, however, remains to be established. It is conceivable, nevertheless, that the suppression of repetitive ventricular ectopy by amiodarone may serve to eliminate the trigger mechanism for the ventricular tachycardia. Furthermore, when ventricular tachycardia does supervene during adequate amiodarone therapy the cycle length of the dysrhythmia is usually long because of a lengthened effective refractory period, and the resulting hemodynamic disturbance is often inconsequential. Both features may be of significance in protecting a patient from the development of ventricular fibrillation, because the latter usually supervenes in the setting of accelerating ventricular tachycardia or deteriorating myocardial function in a patient with underlying cardiac disease.

The overall data with amiodarone emphasize the potential of the drug to enhance survival in patients at risk for recurrent ventricular tachycardia/ventricular fibrillation. Whether other antiarrhythmic agents, such as sotalol and bepridil—which also seem to prolong cardiac repolarization—might be equally effective remains to be determined. In the meantime, a change in the perspective relative to the role of class I versus

class III antiarrhythmics in the control of life-threatening ventricular tachyarrhythmias needs to be critically evaluated.

Our own approach for the drug treatment of life-threatening ventricular arrhythmias takes cognizance of the data discussed above. The exclusion and control of underlying or precipitating causes precedes the development of a therapeutic regimen. In most patients the underlying heart disease is determined (often with cardiac catheterization) and left ventricular ejection fraction measured either by contrast or radionuclide ventriculography. The presence and the nature of the arrhythmia is then documented by multiple Holter recordings or programmed electrical stimulation of the heart, or both, when the patient is not taking antiarrhythmic compounds. The goal of drug therapy is twofold: (1) to suppress spontaneously occurring arrhythmias, especially to eliminate complex ventricular ectopic beats and runs of ventricular tachycardia; and (2) to suppress inducible VT/VF. The available data suggest that the attainment of either goal may represent an adequate therapeutic endpoint for judging long-term antiarrhythmic efficacy. For the present, we initiate therapy on the basis of the Holter and programmed electrical stimulation data from the use of quinidine, procainamide, disopyramide (except in patients with a reduced ventricular ejection fraction) and lidocaine congeners (tocainide and mexiletine).

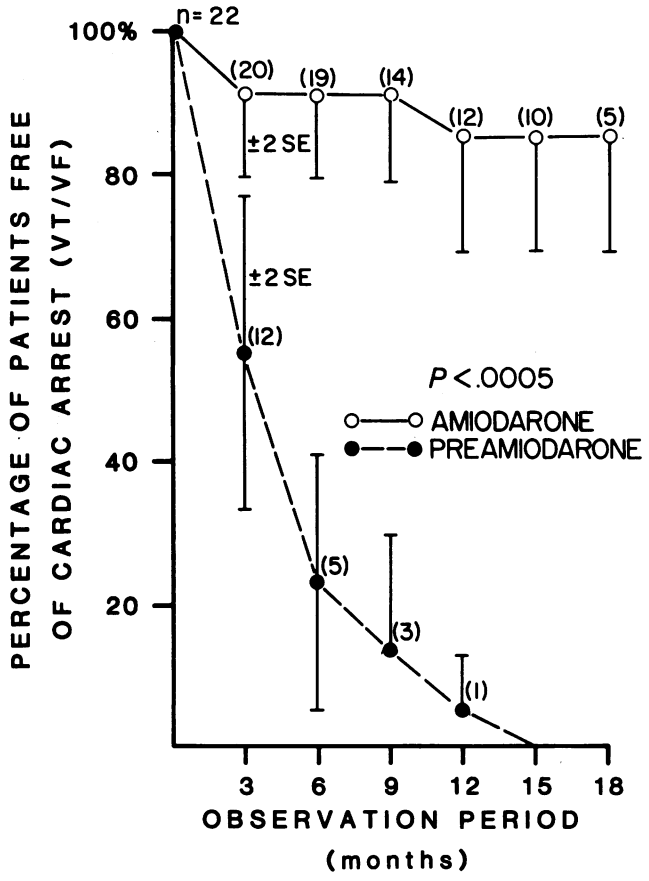


**Figure 11.**—Effect of the use of amiodarone on the recurrence rate of cardiac arrests in 22 patients with a history of one or more episodes before amiodarone therapy. The analysis was by the life-table method for the period of administration. For each period of follow-up, the recurrence rate on the drug regimen was significantly lower. (Based on data from Nademanee et al.[52]) VT/VF = ventricular tachycardia/ventricular fibrillation, SE = standard error.

Phenytoin, β-blockers and calcium antagonists are rarely used except for specific indications. Before considering surgical treatment or implantable devices in patients who fail when treated with conventional drugs,[89-91] investigational agents,[92] particularly amiodarone,[68] are given an exhaustive trial in view of the apparently extraordinary potency of this unusual compound and of the expanding knowledge of its pharmacokinetics and safety features.[93]

## Surgical Treatment of Ventricular Arrhythmias

JOHN H. WITTIG, MD:* Despite considerable advances in our understanding of the mechanisms of clinical ventricular arrhythmias and in surgical techniques, the surgical treatment of ventricular arrhythmias must still be viewed as part of an ongoing investigation in a continuing state of evolution in its various aspects.[94] The main approaches are listed in Table 3.

Sympathetic excitability plays a dominant role in the genesis of ventricular tachycardia in some patients. Thus, from time to time cardiac sympathectomy or denervation has been done in patients with truly refractory ventricular tachycardia.[85] With the advent of β-blockers and other antiarrhythmic compounds, sympathetic ablation is rarely, if ever, done now. However, in some patients with the long QTc-interval syndrome,[37] recurrent VT/VF may occur. In this syndrome, there seems to be an asymmetry between left and right sympa-

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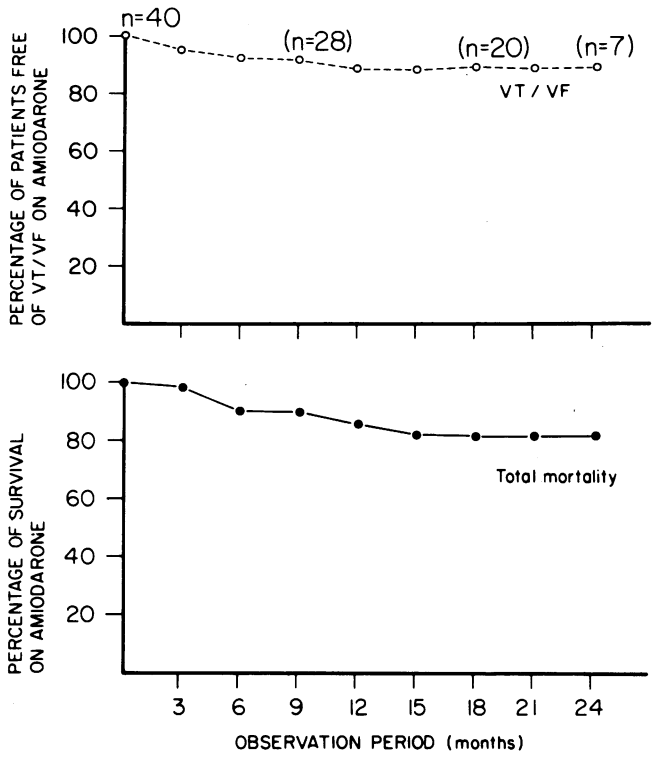


**Figure 12.**—Effect of amiodarone therapy on total mortality (upper panel) and mortality rate from arrhythmias (lower panel) in 40 survivors of cardiac arrests treated with amiodarone over 24 months. The total mortality was 10%, the mortality from arrhythmia less than 5%. The data indicate that amiodarone has the potential to prolong survival in the survivors of cardiac arrests. (Based on data from Nademanee et al.[52]) VT/VF = ventricular tachycardia/ventricular fibrillation.

TABLE 3.—*Surgical Approaches to the Control of Recalcitrant Life-Threatening Ventricular Tachycardia and Fibrillation*

| |
|---|
| Local ablation, for example, local excision of tissue in right ventricular dysplasia |
| Ablation of sources of sympathetic transmitters to the heart |
| Regional cardiac sympathectomy[85] * |
| Left stellate ganglionectomy (for recurrent ventricular tachycardia or ventricular fibrillation in the context of long QTc-interval syndromes)[37] |
| Myocardial revascularization[86] |
| Non-map-guided aneurysmectomy[72] |
| Map-guided endocardial ventriculotomy[87] |
| Map-guided endocardial excision[88] |

*The superscript numbers indicate sources from which detailed information may be obtained.

thetic nerve activity; left-sided cervicothoracic sympathectomy, including stellate ganglionectomy, has been reported to normalize the QT interval and to prevent possibly fatal recurrent ventricular tachyarrhythmias.[37]

Coronary artery bypass grafting has also been suggested as a method for controlling ventricular tachycardia in patients with coronary artery disease. However, numerous reports have suggested that myocardial revascularization, alone or in combination with ventricular resection, is usually not effective in the control of recurrent ventricular tachycardia.[95,96] In contrast, recurrent tachycardia that occurs invariably in association with acute ischemic episodes may be eliminated by successful myocardial revascularization.[86] In general, however, myocardial revascularization has not been effective in the control of most cases of VT/VF in patients with coronary artery disease subject to these dysrhythmias.[86,97] In the past, the first direct surgical approach to the control of ventricular arrhythmias was the resection of a ventricular aneurysm (the presumed focus of the arrhythmia) by Couch in 1959.[98] Subsequent experience continues to be sporadic, but, generally, such a blind procedure, even when combined with myocardial revascularization, has yielded less than optimal results in eliminating VT/VF.[72] In one institution, surgical treatment not based on electrophysiologic mapping resulted in a 42% operative mortality (all from recurrent VT/VF and persistent arrhythmias in seven of eleven survivors).[97]

The recent surge of interest in the surgical treatment of recalcitrant ventricular arrhythmias[72] has followed in the wake of the development of accurate electrophysiologic mapping techniques. These have permitted preoperative and intraoperative location of the earliest focus of origin of ventricular tachycardia and the activation sequence[99,100] during the arrhythmia compared with that occurring after sinus activation. Ventricular tachycardia must be present at operation to permit intraoperative mapping and surgical correction, which is feasible because in most patients ventricular tachycardia seems to be due to a relatively protected focal electrical circuit. It lends itself to surgical correction either by endocardial excision[101] or by encircling endocardial ventriculotomy[87]—the two most promising techniques in the surgical treatment of drug-refractory ventricular tachyarrhythmias. Encircling endocardial ventriculotomy has been used largely by Guiraudon and associates[87] in relatively few patients; their results, while promising, are not striking. Our own experience has been essentially with the technique of map-guided endocardial excision in a limited series of patients. The most extensive experience has been reported by Horowitz and associates.[88] They compared the results of standard aneurysmectomy with those of map-guided endocardial excision in their institution. After a standard aneurysmectomy in 71 patients, ventricular tachycardia either persisted or could be reinitiated in 67 patients. These observations indicated the need for extending the surgical resection beyond the limits of standard aneurysmectomy to include the reentrant circuits. Subsequently, when this was done[98] in 79 patients, 7 deaths caused by pump failure occurred within 30 days of the operation. In 70 (of the 72) patients surviving the procedure, electrophysiologic studies were done before discharge. Ventricular tachycardia could not be induced by programmed electrical stimulation in 55. In the remaining patients antiarrhythmic agents, which were previously ineffective, were given long-term. During a limited follow-up, there have been four recurrences of ventricular tachycardia in the 72 patients. These results are clearly encouraging. They indicate that an electrophysiologically guided cardiac surgical procedure has become an important mode of therapy for refractory ventricular tachycardia; its role, however, needs to be further defined and delineated relative to the newer developments in pharmacologic therapy and those in implantable electronic devices.[8]

## Role of Implantable Defibrillatory and Antitachycardia Devices

PETER M. GUZY, MD, PHD:* An entirely new departure in the control of cardiac dysrhythmias recently has been the concept of an implantable electronic device with the ability to sense and correct malignant ventricular tachyarrhythmias.[8] Although extremely encouraging, most of the implantable antitachycardia devices are still in the early stages of development and restricted to investigational protocol use. Their use, therefore, remains at present restricted to patients with symptomatic ventricular arrhythmias uncontrolled by antiarrhythmic drugs, those unable to tolerate conventional and investigational drugs, those with hemodynamically compromising tachyarrhythmias noninducible by electrophysiologic testing and those who are not candidates for the surgical control of drug-resistant ventricular tachyarrhythmias.

Various pacing techniques have been developed to date to either terminate or prevent tachyarrhythmias.[102-105] Pacing interruption of reentrant tachyarrhythmias requires critical timing to create a zone of refractory tissue that will block further impulse conduction in the reentrant circuit. Implantable devices designated to deliver single or multiple pacing stimuli have been developed, but their effectiveness is limited by the following factors: distance from the pacing electrode to the reentrant circuit, conduction and refractory properties of the intervening cardiac tissues, size of the reentrant circuit and rate of the intrinsic tachycardia.[105] Tachycardias with longer cycle lengths (slower rates) prove to be more amenable to pacing termination compared with the tachycardias with shorter cycle lengths, which are frequently resistant to pacing interruption. In some instances, antiarrhythmic drug therapy will prolong the cycle length enough to enable pacing termination of the tachyarrhythmia.[106] However, pacing stimuli may inadvertently accelerate an otherwise hemodynamically stable tachycardia and result in clinical deterioration or induce ventricular fibrillation, despite concurrent antiar-

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rhythmic therapy.[106-108] Even when meticulous electrophysiologic testing has shown reproducible pacing termination of at least 100 episodes of the patients' tachyarrhythmia before the implantation of an antitachycardia device, unpredictable tachycardia acceleration, or ventricular fibrillation, has been found sporadically.[102] Therefore, implantable antitachycardia devices without defibrillator capability will probably be inadequate for ventricular tachyarrhythmia control in most patients, though these devices may be sufficiently reliable for control of drug-resistant supraventricular tachycardias.

During the past three years, an experimental-status, implantable automatic defibrillator has been undergoing clinical evaluation in a multicenter, investigational protocol.[109] This device automatically delivers a 25-joule discharge between an intravascular electrode positioned in the superior vena cava and an apical epicardial mesh electrode within 20 seconds after detection of ventricular fibrillation. Recent modifications enable this device to also provide R-wave synchronous cardioversion for ventricular tachycardias faster than the preset heart rate limit. Of 52 patients with a mean follow-up of 14.4 months, 17 experienced 62 successful, out-of-hospital conversions of malignant ventricular arrhythmias by the device. The 22.9% total one-year mortality and the 8.5% sudden-death one-year mortality were lower than the predicted 48% mortality for this patient group without an automatic defibrillator.[8] Another automatic defibrillatory device under development uses a transvenous endocardial electrode system to enable R-wave synchronous cardioversion of ventricular tachycardias at low energy output of 2 joules or less.[110,111] Although R-wave synchronous cardioversions have been done successfully at energy outputs as low as 0.008 joules, acceleration of ventricular tachycardia and hemodynamic compromise or initiation of ventricular fibrillation has occasionally resulted. In addition, supraventricular tachyarrhythmias have also been induced occasionally by the cardioversion or defibrillatory discharges, but these supraventricular tachyarrhythmias have tended to be transient.[110]

In conclusion, implantable devices with antitachycardia and defibrillatory capabilities will be used increasingly in the future as an alternative and an adjunct to both drug and surgical therapy for refractory tachyarrhythmias. Incorporation of a backup pacing capability for bradyarrhythmia control, multiprogrammability for noninvasive adjustment of operational settings and telemetry for determining programmed and measured criteria will make these expensive devices more cost-effective. This will likely give physicians greater flexibility in adjusting a device's operative characteristics to changes in a patient's clinical state, thereby possibly reducing both battery drain and repeated hospital admissions. Although the initial reported experience with an implantable automatic defibrillator suggests a reduction in expected mortality, further studies will be required to determine the impact of these devices on overall patient morbidity and mortality and hence their precise role in the management of life-threatening ventricular tachyarrhythmias.

## Conclusion

DR. SINGH: Although data have not been obtained from stringently controlled and blinded protocols, significant inroads may be made into the mortality figure from life-threatening ventricular tachyarrhythmias because of recent advances in antiarrhythmic therapy. New developments have followed closely in the wake of advances in our knowledge of cardiac electrophysiology, particularly the genesis of cardiac arrhythmias. In the clinical laboratory, the relevance of the experimental data may be tested with a particular reference to the nature of clinical arrhythmias and of the fundamental mechanism of action of antiarrhythmic interventions. The newer developments in their wake have raised other questions that provide a fresh impetus for further electrophysiologic and electropharmacologic research.

An antiarrhythmic agent that prevents the induction of VT/VF induced in a controlled state by programmed electrical stimulation may also prevent spontaneous recurrences of the tachyarrhythmia. The data suggest that the converse may not be the case in that the drug amiodarone, an extremely potent suppressant of premature ventricular contractions, so often fails to prevent the induction of VT/VF but provides effective long-term protection against the recurrence of spontaneous arrhythmias in such patients. This does not hold for class I or membrane-active drugs. The fundamental electrophysiologic basis to account for the differences between the response to amiodarone on the one hand and for the class I compounds on the other is not known. Nevertheless, it is a difference that merits study as it may provide further insights into the methods for a more predictable control of malignant ventricular arrhythmias.

Another issue that needs detailed investigation is the relation between a compound's ability to prevent inducible VT/VF and its potency to suppress spontaneously occurring tachyarrhythmias. For example, it is not known whether, in the case of class I agents, it is the same subset of patients in which an effective agent prevents inducible VT/VF and eliminates complex PVCs and runs of ventricular tachycardia in 24-hour Holter recordings. This finding is of immediate therapeutic significance because the available data, discussed in this conference, indicate that both indexes are predictive of long-term efficacy of therapy in life-threatening ventricular tachyarrhythmias. Only a stringently controlled trial in a substantial number of patients followed for a lengthy period is likely to provide a decisive answer. Because an increasing number of newer antiarrhythmic agents with documented potency for near complete suppression of PVCs is becoming available, it is also imperative to establish to what extent PVC suppression may lead to a reduction in the incidence of sudden arrhythmic deaths in patients with heart disease.

The pharmacologic and electrophysiologic advances with the growing therapeutic dividends in their wake must be considered as a continuum with those occurring in the development of surgical techniques and of implantable electronic devices. At present, these modalities are in the early stages of development for the control of ventricular tachyarrhythmias. However, preliminary results from investigations done to date provide cause for the belief that major advances in these areas are likely in the future.

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